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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,060	01/04/2002	Andrew Koff	14538A-005111US	5760

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,060	KOFF ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 10/31/2005 is acknowledged. Claims 1-11 are pending. Claims 1 and 2 were amended. Claims 1-11 are under consideration. The sections of 35 U.S.C. not included in this office action can be found in a previous office action. An action on the merits follows.

Claim Rejections - 35 USC § 112

The rejection of claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, is maintained because the specification, while being enabling for an *ex vivo* method for increasing the proliferation of thymocytes in a non-human animal comprising disrupting an endogenous gene encoding $p27^{Kip1}$, wherein the $p27^{Kip1}$ gene is disrupted by inserting a nucleotide sequence encoding a positive selectable marker in the endogenous $p27^{Kip1}$ gene, mutation or deletion of the endogenous $p27^{Kip1}$ gene, in an isolated thymocyte, or an isolated hematopoietic progenitor cell that differentiates into a thymocyte, from a non-human animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$, re-introducing the altered cells having the functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$ to the donor non-human animal thereby increasing the proliferation of thymocytes in the animal, does not reasonably provide enablement for a method for increasing the proliferation of thymocytes in a non-human animal comprising any method of altering an endogenous gene encoding $p27^{Kip1}$ in an isolated thymocyte, or <u>any</u> isolated multipotent cell from <u>any</u> animal that differentiates into a thymocyte, of the animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$, introducing the altered cells having the functional deficiency of cyclin-

dependent kinase inhibitor function of $p27^{Kip1}$ to any non-human animal of any species thereby increasing the proliferation of thymocytes in the animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 10/31/2005 have been fully considered but they are not persuasive. The previous office action identified the following issues of record: **1)** failure to enable an *ex vivo* method of gene therapy using embryonic stem cells; **2)** failure to provide guidance on the administration of xenogeneic cells or allogeneic cells; and **3)** failure to recite any particular threshold for targeting specificity or of therapeutic efficacy for any method of disrupting a $p27^{Kip1}$ gene. Applicant's amendments to the claims and arguments presented have overcome the rejection based on issues **1** and **3**.

2) Applicant argues that the presence of inoperative embodiments within the scope of a claim does not render a claim nonenabled. Further applicant argues that xenogeneic transplant rejection is a factor well-understood in the art and that the skilled artisan would readily understand whether such an embodiment is inoperative or operative. However, this is not considered to be persuasive. As previously stated: The claims encompass the administration of xenogeneic, allogeneic and autologous cells of hematopoietic origin. The specification does not teach that any thymocyte or any isolated multipotent cell, with or without a $p27^{Kip1}$ gene are sufficient to over come the immune system mediated hyperacute rejection of xenogeneic tissues due to differences in surface carbohydrate moieties among different species. The hyperacute rejection of xenotransplants is mediated by antibody response to differences in surface protein

carbohydrate modifications and, not MHC expression. Gojo et al. teaches that the T cell response to porcine xenotransplants is secondary to the natural immune barrier of hyperacute rejection of porcine tissues due to the Gal α moiety {Gojo et al. (2000) Transplantation. 69:1995-1999; pgph 12}. Further, the specification does not disclose that the thymocyte or isolated multipotent cell are typed for MHC mismatches prior to administration. MHC mismatches between different tissues triggers NK, T cell and antibody mediated paths of rejection. The specification does not disclose any working examples that describe administration of any thymocyte or any isolated multipotent cell with a disruption in the $p27^{Kip1}$ gene are capable of preventing rejection.

Further, the claims are examined to the broadest scope that is reasonably encompassed by the claim language. Claim 1 continues to reasonably encompass administration of allogeneic and xenogeneic cells to any non-human animal. Typically, inoperative embodiments are excluded by language in a claim (e.g.,preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. As stated above and in the prior office action it would require undue experimentation to determine which allogeneic and xenogeneic cells could be administered to any specific non-human animal in order to practice the claimed invention. For the reasons of record stated above, and in the previous action of 4/19/2005, the rejection over issue **2** is maintained.

Claim Rejections - 35 USC § 102

The rejection of claims 1-11 under 35 U.S.C. 102(e) as being clearly anticipated by Roberts JM et al (US Patent No 5,958,769, dated 8-28-99, filing date 1-18-1996), is maintained.

Response to Arguments

Applicant's arguments filed 10/31/2005 have been fully considered but they are not persuasive. Applicant has amended claim 1 to recite the step of monitoring the animal to detect the increase in thymocyte proliferation. Further, they argue that while Roberts et al. discloses the counting of nucleated cells from the thymus and the spleen this is somehow different from monitoring the animal to detect the increase in thymocyte proliferation. This is not found persuasive.

Roberts et al. teaches that the examined thymus and spleen were twice as large as control mice and that counts of nucleated cells from the spleen and thymus confirmed the hypercellularity of these tissues. By monitoring the increase in nucleated cells in the thymus, Roberts et al. is literally detecting an increase in thymocytes, and is thus detecting an increase in thymocyte proliferation as encompassed by the amended claims. For the reasons of record stated above, and in the previous actions of 4/19/2005, 11/07/2003 and 7/28/2004, the rejection is maintained.

No claims allowed

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application

status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
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